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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,808	11/14/2003	Dave S.B. Hoon	89212.0014	4483

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,808	HOON ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10 and 31-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/13/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 5/13/08 in response to the Office Action of 12/13/07 are acknowledged and have been entered.

Claims 1-7, 10, and 31-35 are pending.

Claim 31 has been amended by Applicant.

Claims 1-7, 10, and 31-35 are currently under examination.

Terminal Disclaimer

The terminal disclaimer filed on 5/13/08 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on Application No. 11/227575 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Information Disclosure Statement

Only the English portions of the following documents listed in the information disclosure statement (IDS) submitted on 5/13/08 have been considered: WO 99/10528; Kocher et al ("identification of Genes Differentially Expressed in Melanoma Sublines Derived from a Single Surgical Specimen Characterized by Different Sensitivity to Cytotoxic T-lymphocyte Activity," Dept. of Surgery, Z.L.F., 617-624).

Rejections Withdrawn

The provisional rejection of claims 1-7, 10, and 31-34 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-16 of copending application number 11/227575, is withdrawn in view of the Terminal Disclaimer filed 5/13/08.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-33 remain rejected under 35 U.S.C. 103(a) for being unpatentable over Palmieri et al (March 2001, Journal of Clinical Oncology, 19(5):1437-1443) in view of Scholl et al (February 2001, Cancer Research, 61:823-826) and Kuo et al (February 1998, Clinical Cancer Research, 4:411-418) for the reasons stated in the Office Action of 1/31/07, the Office Action of 9/20/07, the Office Action of 12/13/07, and for the reasons set-forth below.

The Office Action of 12/13/07 contains the following text:

"The claims are drawn to methods comprising detecting the mRNA expression of a panel of marker genes comprising GalNAcT and/or PAX3 in a SLN sample histopathologically negative for melanoma cells.

Palmieri et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase (pages 1438-1439, in particular).

The methods taught by Palmieri et al comprise methods wherein the sentinel lymph node samples are histopathologically negative for melanoma cells (paragraph bridging the left and right columns of page 1438), wherein the histopathology is determined by hematoxylin and eosin staining and immunohistochemistry. Palmieri et al further teaches, and one of skill in the art would recognize, that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells (page 1441 right column, in particular).

Palmieri et al does not specifically teach methods of detecting metastatic melanoma cells comprising isolating nucleic acids from sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MAGE-A3, GalNAcT and/or PAX3. However, these deficiencies are made up in the teachings of Scholl et al (February 2001, Cancer Research, 61:823-826) and Kuo et al (February 1998, Clinical Cancer Research, 4:411-418).

Scholl et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising PAX3, MAGE-A3, and tyrosinase and detecting the presence or absence of the nucleic acid targets (Table 1 and Table 2, in particular).

Kuo et al teaches methods of detecting metastatic melanoma cells comprising isolating nucleic acids from a biological sample obtained from a patient, amplifying nucleic acid targets from a panel of marker genes comprising GalNAcT and detecting the presence or absence of GalNAcT (page 413 right column, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to detect metastatic melanoma cells comprising a method of isolating nucleic acids from histopathologically negative sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase as taught by Palmieri et al and also amplify any other genes associated with metastatic melanoma, such as those taught by Sholl et al (PAX3 and MAGE-A3) and Kuo et al (GalNAcT). Further, one would have been motivated to do so because multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since detection of genes is well known and conventional in the art."

In the Reply of 7/31/07, Applicant argues that none of the cited references disclose detection of GalNAcT or PAX3 in histopathologically negative SLN samples. Applicant further states that Examiner's assertion that there would be a reasonable expectation of success in detecting GalNAcT or PAX3 in histopathologically negative SLN samples has no basis in the cited art and there would not have been a reasonable expectation of success in detecting PAX3 or GalNacT in histopathologically negative SLN samples from melanoma patients. Applicant further argues that Palmieri, Scholl, and Kuo do not indicate that GalNAcT or PAX3 would share the same expression pattern as Tyrosinase and MART-1 simply because they are melanoma markers.

Applicant further agues that it is well known in the art that not all genes are detectable in all type of samples and that a melanoma marker detected in one type of sample from a melanoma patient is not necessarily detectable in another type of sample from melanoma patients. Applicant further states that Kuo demonstrates that while GalNAcT is detectable in blood samples form AJCC stage II, III, or IV melanoma patients, it is not detectable in blood samples from AJCC stage I melanoma patients. Applicant further states that detection of PAX3 in cultured primary melanomas and their corresponding tissue sections and the detection of GalNAcT in melanoma cell lines, primary biopsies, histopathologically positive tumor-draining lymph node (TDLN) metastasis, distal organ metastasis, and blood do not indicate that GalNAcT and PAX3 would be detectable in histopathologically negative SLN samples from melanoma patients.

The arguments found in the Reply of 7/31/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that none of the cited references disclose detection of GalNAcT or PAX3 in histopathologically negative SLN samples, the Examiner agrees that none of the cited references disclose detection of GalNAcT or PAX3 in histopathologically negative SLN samples. However, motivation to detect GalNAcT and PAX3 in histopathologically negative SLN samples is discussed above. Specifically, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to detect metastatic melanoma cells comprising a method of isolating nucleic acids from both histopathologically negative and histopathologically positive sentinel lymph node samples obtained from a patient, using RT-PCR to isolated nucleic acids and amplify mRNA targets from a panel of marker genes comprising MART-1 and tyrosinase as taught by Palmieri et al and also amplify any other transcripts of genes expressed by metastatic melanoma cells, such as those taught by Sholl et al (PAX3 and MAGE-A3) and Kuo et al (GalNAcT) and one would have been motivated to do so because Palmieri et al teaches and one of skill in the art would recognize that multiple-marker assays are more sensitive and specific than single-marker assays in detecting metastatic melanoma cells.

In regards to the argument that Examiner's assertion that there would be a reasonable expectation of success in detecting GalNAcT or PAX3 in histopathologically negative SLN samples has no basis in the cited art, there would be an expectation of success in detecting levels of GalNAcT or PAX3 (both levels indicative of no transcripts and levels indicative of GalNAcT or PAX3 transcripts) because Sholl et al teaches methods of detecting levels of PAX3 transcripts and Kuo et al teaches methods of detecting levels of GalNAcT transcripts.

Further, in regards to the argument that Palmieri, Scholl, and Kuo do not indicate that GalNAcT or PAX3 would share the same expression pattern as Tyrosinase and MART-1 simply because they are melanoma markers and it is well known in the art that not all genes are detectable in all type of samples and that a melanoma marker detected in one type of sample from a melanoma patient is not necessarily detectable in another type of sample from melanoma patients, one of skill in the art would expect differential expression of GalNAcT, PAX3, Tyrosinase, and MART-1 in metastatic melanoma cells because Palmieri, Scholl, and/or Kuo teach that GalNAcT, PAX3,

Tyrosinase, and MART-1 are differentially expressed in metastatic melanoma cells (note that metastatic melanoma cells are a single type of sample).

In the Submission of 10/31/07, Applicant states that it is Applicant's discovery that GalNAcT and PAX3 are expressed in histopathologically negative SLN samples from melanoma patients. Applicant further states that without such knowledge, one skilled in the art would not have been motivated to use GalNAcT or PAX3 as a gene marker when analyzing histopathologically negative SLN samples from melanoma patients. Applicant further states that since none of the three cited references disclose detection of GalNAcT or PAX3 in histopathologically negative SLN samples from melanoma patients, one skilled in the art would not have reasonably expected that mRNA transcripts encoded by GalNAcT and PAX3 can be detected in histopathologically negative SLN samples from melanoma patients.

The arguments found in the Submission of 10/31/07 have been carefully considered, but are not deemed persuasive. In regards to statements that it is Applicant's discovery that GalNAcT and PAX3 are expressed in histopathologically negative SLN samples from melanoma patients, methods comprising detecting GalNAcT and PAX3 in histopathologically negative SLN samples from a melanoma patient are anticipated by the *combined* teachings cited above. For example, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to diagnose metastatic melanoma by detecting melanoma cells comprising a method of isolating nucleic acids from both histopathologically negative and histopathologically positive SLN samples obtained from a patient, using RT-PCR on isolated nucleic acids and amplifying mRNA targets from a panel of genes comprising MART-1 and tyrosinase as taught by Palmieri et al and also amplify any other transcripts of genes known to be expressed by metastatic melanoma cells, such as those taught by Sholl et al (PAX3 and MAGE-A3) and Kuo et al (GalNAcT), and one would have been motivated to do so because Palmieri et al teaches, and one of skill in the art would recognize, that multiple-marker assays are more sensitive and specific as compared to single-marker assays in detecting metastatic melanoma cells for diagnosing metastatic melanoma."

In the Reply of 5/13/08, Applicant has added in claim 31: "...wherein the levels of the mRNA transcripts are indicative of the presence of mRNA transcripts encoded by GalNAcT, PAX3, or both". Applicant further argues that even if one in the art would have been motivated to examine GalNAcT or PAX3 expression in histopathologically negative SLN samples with a reasonable expectation of detecting some levels of GalNAcT or PAX3 mRNA transcripts, one skilled in the art would not have reasonably

expected that detected levels of GalNAcT or PAX3 mRNA are indicative of the presence of GalNAcT or PAX3 mRNA transcripts, because each gene has a unique expression pattern and none of the cited references suggests the expression of GalNAcT or PAX3 in histopathologically negative SLN samples from melanoma patients.

The amendments to the claims and the arguments found in the Reply of 5/13/08 have been carefully considered, but are not deemed persuasive. In regards to the argument that one skilled in the art would not have reasonably expected that detected levels of GalNAcT or PAX3 mRNA in histopathologically negative SLN samples are indicative of the presence of GalNAcT or PAX3 mRNA transcripts, because each gene has a unique expression pattern and none of the cited references suggests the expression of GalNAcT or PAX3 in histopathologically negative SLN samples from melanoma patients, one would have expected that detected levels of GalNAcT or PAX3 mRNA in any sample are indicative of the presence of GalNAcT or PAX3 mRNA transcripts in said sample because the cited art teaches detected levels GalNAcT and PAX3 mRNA transcripts are indicative of the presence of GalNAcT and PAX3 mRNA transcripts (see Table 1 and Table 2 of Scholl et al and page 413 right column of Kuo et al, in particular). Further, it is noted that the added "wherein" clause of claim 31 is not an active method step.

Allowable Subject Matter

Claims 1-7, 10, 34, and 35 are allowed.

Summary

Claims 31-33 are rejected.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Examiner, Art Unit 1642